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Synergetic delivery systems for active molecules

Background of the invention

1. Field of the invention.

The present invention relates to drug delivery, particularly transdermal drug delivery, and therapy devices for a patients by means of various sources of energy and their combination such as sound/ultrasound, iontophoresis, magnetophoresis, electromagnetic waves and also including the combination of aerosol particles with aforesaid kinds of energy.

2. Description of the Prior Art.

Transdermal drug delivery systems are well known in the prior art. There are two methods by which drugs can be delivered through the skin: passive diffusion and active transport. Passive diffusion involves placing a concentration of a drug over the surface of the skin and allowing the drug to diffuse through the skin. Due to the natural skin barriers, few pharmaceuticals with sufficiently small molecular size have been successfully passively diffused into the body. Examples are nicotine and nitroglycerin delivered by patch devices.

A more viable way for drugs to penetrate the skin's barriers is by means of an active energy source that pushes drug molecules through the skin. That allows a greater quantity of medicine and medicine of a greater molecular size to be delivered in a shorter time frame. There are several types of active transdermal drug delivery systems: iontophoresis, electroporation, phono/sonophoresis, magnetophoresis, electromagnetophoresis etc.

Numerous attempts have been made in the past to deliver medications through the skin by electrical and ultrasonic means.

The application of electrical fields to create transient transport is known as electroporation, and the method to electrically transport charged drug molecules through the skin is known as iontophoresis.

Electroporation creates transient pores in the lipid bilayers of the stratum corneum, the outermost layer of skin. Iontophoresis provides an electrical driving force to move charged compounds.

Electroporation involves application of electric field pulses that create transient aqueous pathways in lipid bilayer membranes, causing a temporary alteration of skin structure. While occurrence of aqueous pores may allow transdermal permeation of neutral molecules by diffusion, the transport of charged molecules during pulsing occurs predominantly by electrophoresis and electroosmosis.

Iontophoresis has been used to increase the permeability of skin to drugs, and involves the application of an external electric field, and topical delivery of an ionized form of drug (or of a neutral drug carried with the water flux associated with ion transport, i.e., via "electroosmosis"). While permeation enhancement via iontophoresis has, as with chemical enhancers, been effective, there

are problems with the degree of irreversible skin damage induced by the transmembrane passage of current.
Besides, ionophoresis tends to work only if the molecules can be dissociated into positive and negative ions and then driven in. A primary disadvantage of this technique is that many drugs cannot be dissociated. Another disadvantage is that many drugs lose their effectiveness if broken up in this manner.

Electroporation and iontophoresis have both been proven ineffective to deliver therapeutically adequate dosages of many medications through the skin.

The effects of sonophoresis on skin result from the release of energy. These include the non-thermal effects of cavitation, and mechanical stress as well as thermal effects.

It appears that ultrasound exposure in the therapeutic range causes cavitation in the keratinocytes of the stratum corneum as the primary effect in increasing skin permeability for transcutaneous transport of topical agents (cavitation is a process where bubbles are formed which may oscillate or collapse, causing structural disorder of the intercellular lipid bilayers of the keratinocytes).

In effect, this process is somewhat analogous to loosening the "mortar between the bricks" and expanding the "spaces between these bricks" so that the topical agent has a transport pathway to reach the epidermis and the deeper dermis of the skin. Drug molecules that are too large to penetrate the skin at all when applied topically may achieve significant penetration when used in conjunction with sonophoresis with proper parameters.

Sonophoresis has been shown to enhance transdermal transport of various drugs. Although a variety of ultrasound conditions have been used for sonophoresis, the most commonly used conditions correspond to the therapeutic ultrasound (frequency in the range of 1 MHz-3 MHz, and intensity in the range of 0-2 W/cm^2).

In spite of these advantages, very few drugs and no proteins or peptides are currently administered transdermally for clinical applications because of the low skin permeability to drugs. Application of therapeutic ultrasound does not induce transdermal transport of high-molecular weight proteins. It is a common observation that the typical enhancement induced by therapeutic ultrasound is less than ten-fold. In many cases, no enhancement of transdermal drug transport has been observed upon ultrasound application. This low permeability is attributed to the stratum corneum (SC), the outermost skin layer which consists of flat, dead cells filled with keratin fibers (keratinocytes) surrounded by lipid bilayers. The highly-ordered structure of the lipid bilayers confers an impermeable character to the SC (Flynn, G. L., In Percutaneous Absorption: Mechanisms-Methodology-Drug Delivery; Bronaugh, R. L., Maibach, H. I. (Ed), pages 27-53, Marcel Dekker, New York, 1989).

Accordingly, a better selection of ultrasound parameters is needed to induce a higher enhancement of transdermal drug transport by sonophoresis. Moreover, although efficacy to some degree has been observed using ultrasound for transport of other compounds, the efficiency of transport under conditions acceptable to patients has not been achieved.

Application of low-frequency (20 kHz) ultrasound dramatically enhances transdermal transport of drugs. Transdermal transport enhancement induced by low-frequency ultrasound was found to be as much as 1000-fold higher than that induced by therapeutic ultrasound (frequency in the range of 1 MHz-3 MHz, and intensity in the range of 0-2 W/cm^2). Another advantage of low-frequency sonophoresis as compared to therapeutic ultrasound is that the former can induce transdermal transport of drugs, which do not passively permeate across the skin. Application of low-frequency ultrasound appears to induce cavitation inside as well as outside the skin. Cavitation occurring at either location may cause disordering of the SC lipids. In addition, oscillations of cavitation bubbles may result in significant water penetration into the disordered lipid regions. This may cause the formation of aqueous channels through the intercellular lipids of the SC. This allows permeants to transport across the disordered lipid domains, then across keratinocytes and the entire SC. This transport pathway may result in an enhanced transdermal transport as compared to passive transport because the diffusion coefficients of permeants through water, which is likely to primarily occupy the channels generated by ultrasound, are up to 1000-fold higher than those through the ordered lipid bilayers, and the transport path length of these aqueous channels may be much shorter (by a factor of up to 25) than that through the tortuous intercellular lipids in the case of passive transport.

Studies of the safety of low frequency ultrasound, which creates the cavitation effect, showed that only low intensities could be safe.

Application of a magnetic field to the skin induces enhanced tissue permeability consequent upon the application of the variable field. This magnetophoretic effect increases efficiency of delivery due to the action of the magnetic field on the charged particles of the ionic drug. This method is very safe and can be efficient if the drug has penetrated through the epidermis. Magnetophoresis is limited by the inability of the field to achieve transport through the epidermis. Therefore this method could be applicable for drug delivery to eye or through the mucous membranes.

In some cases, high strengths of the physico-chemical forces (for example, electricity, ultrasound) are required to deliver a given drug dose transdermally. However, the highest strength of these physico-chemical forces that can be used is limited by their adverse physiological effects.

Application of magnetic fields to the skin pretreated with ultrasound may also result in a higher transport of magnetically active species across the skin. For example, polymer microspheres loaded with magnetic particles could be transported across the skin using sonophoresis and magnetic fields.

Transdermal transport of molecules during sonophoresis can be further enhanced by simultaneous application of an electric field, for example, by iontophoresis or by electroporation and magnetic fields. This synergy of energies could dramatically reduce the physico-chemical forces required for drug delivery.

The Russian Patent "Apparatus for electrophoresis" (#733,693 of 15.05.1980) describes the method and device for enhancement of the drug delivery to the root channel by combined action of **ultrasound and iontophoresis.**

The US patent "Submersive therapy apparatus" (#5,741,317 of 21.05.1998) describes an apparatus for therapy, which includes **ultrasound, electric and electromagnetic fields** radiated/delivered from different devices. This combination enhanced the efficiency of treatments.

The US patent "Electrophoretic cuff apparatus drug delivery system" (#5,983,134 of 09.10.1999) describes the apparatus, which can provide electromagnetophoresis. Scientific information supports the concept that electromagnetic fields (EMFs), in combination with *drug delivery*, can either increase the osmotic penetration of drugs through the skin known as "*magnetophoresis*", or that EMFs may help accelerate the effectiveness of exogenous drugs after being introduced into the body by transdermal or hypodermic methods. Exposure to PMF (Pulsed Magnetic Field) immediately after administration of methotrexate or mitomycin C, pharmaceutical antitumour agents, into the cell increases eddy current stimulation induced by PMF, and the cell cycle shifts from the non-proliferate to proliferative phase, resulting in increased anti-tumour activity.

Another object of this invention is to provide combined therapy, where the combination of **magnetotherapy, electrotherapy and iontophoresis** heightens the effectiveness of electrochemotherapeutic treatment to a target area used for electrochemotherapy (ECT). The combination of multiple drivers to produce an electrochemotherapeutic effect is known as "electro-infusion".

Magnetic fields induce an electrical field within the tissue, which is perpendicular to the magnetic field. This increases the internal electrical field strength, thereby increasing the penetration factor without increasing the externally applied current. This method produces a homogeneous potential layer.

The US Patent "Automated transdermal drug delivery system" (#6,009,346 of 28.10.1999) describes a device for automated transdermal robotic treatment and a drug delivery system to provide multimodal therapies and treatments to a patients. The treatment is energized from a console to deliver modes of ultrasound therapy, electrotherapy, sonophoresis, and iontophoresis. All sources of therapies/drug delivery are separate, discrete and independent devices or probes, which can operate independently or in different combinations.

The combination of the sources of energy significantly enhances the efficiency of delivery.

At the same time, use of low-frequency ultrasound of high intensity for inducing cavitation represents a serious problem for the health of the patient. In addition to a destructive action on the surface of the skin, the low-frequency ultrasound (due to the small attenuation) is capable of deeply penetrating into an organism, rendering serious damage. There is data on serious diseases of researchers, chronically exposed to low-frequency ultrasound, including by disinfection of the hands in an ultrasonic bath.

Therefore replacing low frequency ultrasound with a spectrum in the mid-frequency range (higher than100 KHz), where the level of cavitation is small and attenuation of ultrasound is great, will significantly reduce the negative effects described above. However, increasing the ultrasound frequency at constant intensity reduces the efficiency of delivery of medicines.

Summary of the invention

All above described devices utilize different combinations of the sources of energy, which are not combined in a single probe. Therefore the optimal synergetic effect on drug delivery could not be achieved.

To achieve optimum efficiency one should construct the drug delivery probe such that all/part the fields that interact to enhance drug delivery components are concentrated in the same region of space. In this case the maximum combined energy of the drug delivery system will be concentrated into the delivery area and the synergetic effect is optimized.

An especially attractive approach is the combination of magnetophoresis with delivery of a drug to the skin in the form of a nebulized aerosol. Both magnetophoresis and aerosol delivery do not require any direct contact of any apparatus to the skin itself, as both magnetic fields and the nebulized drug particles can propagate through air. This is particularly advantageous in situations when the skin should not be directly contacted, such as in treatment of highly traumatized tissue as in wounds or burns.

Below are presented several examples of the synergetic devices for drug delivery. The optimal efficiency is obtained when all the sources of energy are coaxial.

Brief description of the drawings

Fig. 1 illustrates the perspective view of the transdermal drug delivery/therapy device for sono-electro-magnetophoresis with one or two resonant acoustic frequencies, without a metal concentrator.

Fig. 2 illustrates the perspective view of the transdermal drug delivery/therapy device for sono-electro-magnetophoresis with one or two resonant acoustic frequencies, with a metal concentrator.

Fig. 3 illustrates the perspective view of the transdermal drug delivery/therapy device comprising sono-magneto-iontophoresis with an electroporation part, and compartment for holding a unit dose of the drug to be delivered.

Fig. 4 illustrates the perspective view of the drug delivery device in which the surface area of the delivered chemicals is increased by transformation into aerosol form and enhancement by magnetic field.

Legend for Fig.1, Fig. 2, Fig. 3, Fig. 4

1. Electroacoustic/ultrasonic transducer
2. Silver electrode of an electroacoustic/ultrasonic transducer
3. Piezoceramic of an electroacoustic/ultrasonic transducer
4. Silver electrode of an electroacoustic/ultrasonic transducer
5. Magnetic inductor
6. Electronic generator for magnetic inductor
7. Electronic generator for electroacoustic transducer
8. Electric current generator

9. Metal electrode
10. Skin to be treated
11. Concentrator
12. Electrodes for electroporation
13. Electric generator for electroporation
14. Compartment for drug
15. A nebuliser
16. An aerosol chamber

Description of the invention

The synergetic-type drug delivery device (SDDD) comprising sono-magneto-iontophoresis units incorporating in one construction to create the maximum synergetic effect is shown in **fig. 1**.
The device consists of the electro acoustical transducer 1 made of piezoceramics 2, covered by metal electrodes 1 and 3 on the both side of piezoceramics. The transducer can operate at two frequencies. At the low/mid frequency the transducer can induce cavitation for drug delivery. At the second significantly higher frequency, no cavitation is induced. The transducer connects to a dual-frequency ultrasonic generator 6 compatible with the transducers.
The transducer is constructed of diamagnetic material and is transparent to the magnetic fields produced by the inductor 14. The inductor connects to the electronic generator 5, which produces different forms of voltage to create different types of magnetic fields, including an asymmetric pulse magnetic field.

In **fig. 2** is shown SDDD, which utilizes an ultrasonic transducer 1 with an energy concentrator 11. If the concentrator is constructed from a metal having ferromagnetic properties the concentration of the magnetic field will be significantly enhanced in a volume coaxial with the acoustical field. The inductor 5 is mounted on the concentrator and driven by electronic generator 6. The other parts of the device are the same as in Fig. 1.

In **fig. 3** is shown SDDD, comprising sono-magneto-iontophoresis with an electroporation part and compartment 14 for holding a unit dose of a drug to be delivered.
The electroporation part consists of an electric generator 13 and electrodes 12.
The electrodes are made of a ferromagnetic material to concentrate and transport magnetic energy to the treated surface. The drug to be delivered also serves as a transmission media for ultrasonic energy.

In **fig. 4** is shown SDDD, in which the surface area of the delivered chemicals is increased by transforming it to aerosol form by a nebuliser 15. The efficiency of aerosol delivery is enhanced by the magnetic field 5. Aerosol originating from the nebuliser could be uncharged or have an electrical charge. In the latter case nebulisation could occurs in a strong acoustical field (e.g. nebulisation in the fountain), the charge could be induced by an external electrical field, or by some other means. This magnetic field passes through the aerosol chamber 16 to the surface to be delivered. This idea can also be applied to any aerosol sterilisation/disinfection device.

Dr. Vladimir Sheiman

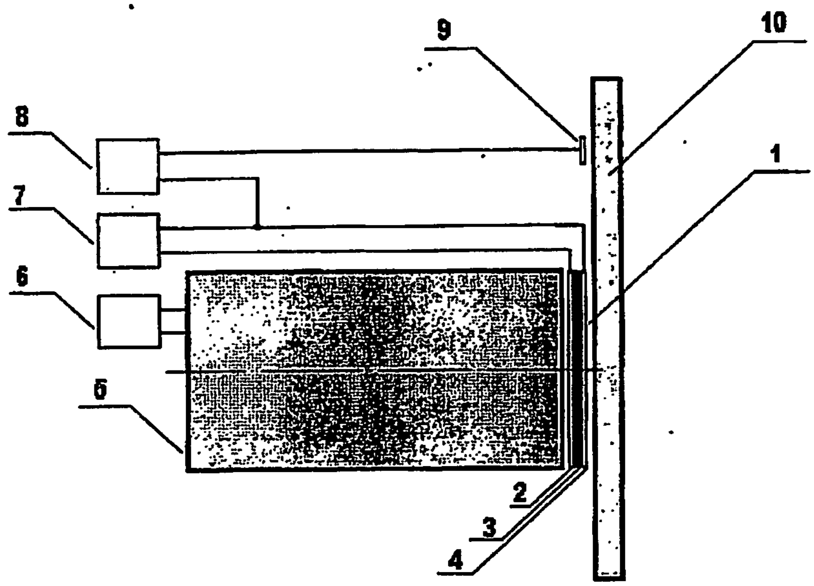

Fig. 1

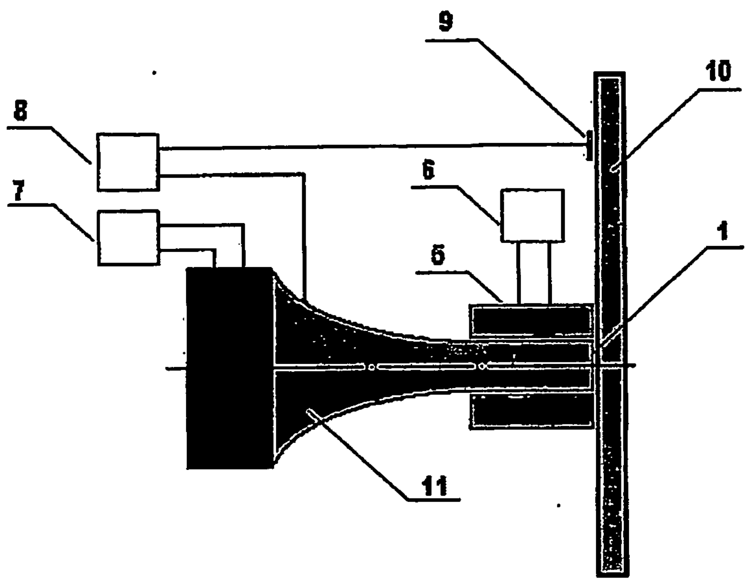

Fig. 2

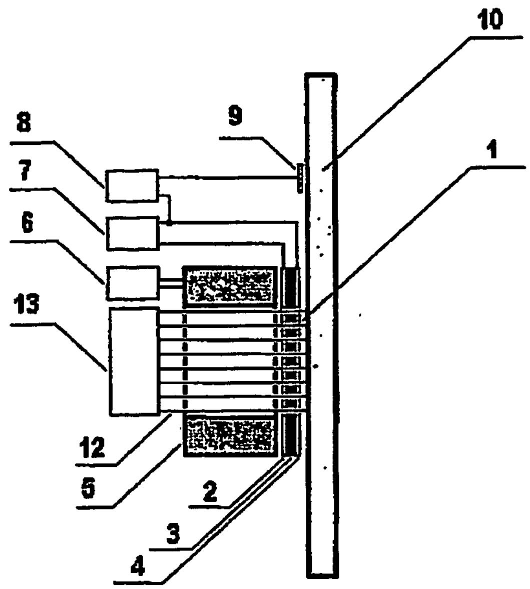

Fig. 3

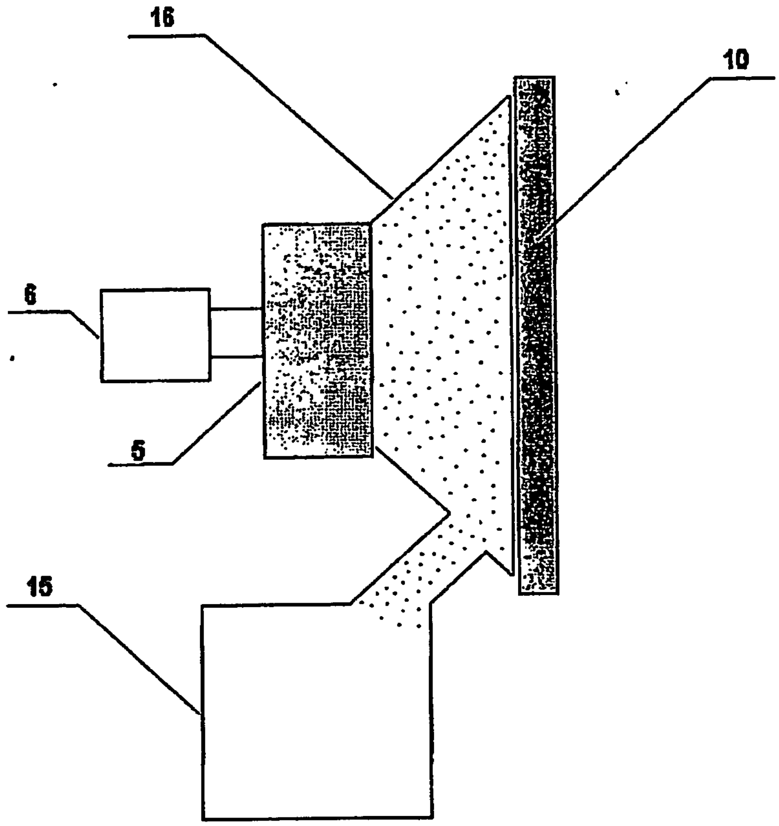

Fig. 4